30. The method of Claim 28 wherein the human mesenchymal stem cells are autologous to the host.

31. The method of Claim 28 wherein said mesenchymal stem cells do not produce co-stimulatory molecules.

B1 32. The method of Claim 28 wherein said mesenchymal stem cells are genetically engineered to express a molecule to block co-stimulation of T-cells.

33. The method of Claim 32 wherein the molecule is membrane-bound.

34. The method of Claim 33 wherein the molecule is CTLA-4.

35. The method of Claim 32 wherein the molecule is a soluble protein.

36. The method of Claim 35 wherein the molecule is CTLA-4-Ig fusion protein.

REMARKS

The claims have been amended in order to place the application in better form.

Claims 17-20 have been cancelled without prejudice and Claims 21-36 have been added. The fact that Claims 17-20 have been cancelled without prejudice is not to be construed as an admission by Applicants or Applicants' attorneys that such claims are not patentable, and Applicants reserve the right to prosecute such claims in a continuing application.

The claims stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is respectfully traversed.

The present invention is directed to a method of inhibiting a T-cell response to an antigen. The method comprises modifying mesenchymal stem cells to present the antigen by contacting the mesenchymal stem cells with the antigen *in vitro* or by genetically engineering the

mesenchymal stem cells to express the antigen. The mesenchymal stem cells do not produce co-stimulatory molecules in a sufficient amount to activate T-cells. The mesenchymal stem cells process the antigen into an antigen fragment for presentation by the mesenchymal stem cells. The modified mesenchymal stem cells then are administered to a host, thereby inhibiting a T-cell response to the antigen upon subsequent exposure of the T-cells to antigen presenting cells which express co-stimulatory molecules.

Support for the invention as claimed broadly is found in the specification in the last paragraph of Page 4 and the first and last paragraphs of Page 5.

The Examiner has stated that the specification provides insufficient evidence that after contacting mesenchymal stem cells (MSCs) in vitro with an antigen, the MSCs of the claimed method would process the antigen into an antigen fragment for presentation by the MSCs.

The Examiner bases his rejection in part upon the Janeway reference. Janeway was published in 1994. Janeway merely does not mention mesenchymal stem cells as an example of cells which may be used to present antigens to T-cells in order to inhibit or lessen a T-cell response to an antigen. Janeway merely did not contemplate such a use for mesenchymal stem cells in 1994. Janeway did not state that mesenchymal stem cells could not be used to present antigens to T-cells in order to inhibit a T-cell response.

Subsequent to the Janeway publication, it was demonstrated that mesenchymal stem cells which produce or express co-stimulation molecules could present an antigen to T-cells. Applicants submit with this Amendment copies of Keane-Moore, et al., Blood, Vol. 92, No. 10, Supplement 1, Abstract 1388 (November 15, 1998) and U.S. Patent No. 6,149,906, issued to Mosca.

Keane-Moore discloses that human mesenchymal stem cells, transduced with gene sequences encoding either B7-1 or B7-2 co-stimulatory molecules, successfully presented tetanus toxoid to a T-cell line when the human mesenchymal stem cells were pulsed exogenously or transduced with a retrovirus expressing tetanus toxin fragment C.

Mosca, in Example 1, discloses that mesenchymal stem cells transduced with gene sequences encoding the co-stimulatory molecules B7-1 and B7-2, and pretreated with Interferon-gamma can be effective antigen presenting cells (In this case the TetC antigen was presented.) in order to induce a T-cell response.

Thus, it had been demonstrated that mesenchymal stem cells which produce or express co-stimulatory molecules can be used as antigen presenting cells for inducing a T-cell response to an antigen.

In Example 1 of the above-identified application, Applicants have shown that mesenchymal stem cells, which do not produce co-stimulatory molecules in a sufficient amount to activate T-cells, can process and present antigens or fragments to T-cells in order to induce tolerance to such antigens. In fact, the Examiner has admitted that T-cell hyporesponsiveness with tetanus toxoid has been shown by Applicants. Applicants, through Example 1, have proven the principle that mesenchymal stem cells, which do not produce co-stimulatory molecules in a sufficient amount to activate T-cells, can process, and present antigens or fragments thereof, to T-cells in order to induce tolerance to the antigens. One skilled in the art would expect reasonably that T-cell hyporesponsiveness would be effected with other antigens as well.

Applicants, through Example 1, demonstrated that mesenchymal stem cells can be pulsed with an antigen, and that such pulsed mesenchymal stem cells can present such antigen or fragment thereof to T-cells in order to induce tolerance to the antigen upon subsequent encounter

of the T-cells with professional antigen presenting cells presenting the antigen or a fragment thereof. Thus, Applicants' discovery is not of such a speculative, abstruse, or esoteric nature that it must be considered unbelievable, incredible, or factually misleading. (See In Re Gazave, 154 U.S.P.Q. 92 (C.C.P.A. 1967), at 96.) The Examiner, therefore, has not met his burden in showing that the specification does not provide an enabling disclosure. For the above reasons and others, this application is in condition for allowance, and it is therefore respectfully requested that the rejection under 35 U.S.C. 112, first paragraph, be reconsidered and withdrawn and a favorable action is hereby solicited.

Respectfully submitted,

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